Abstracts

Minisymposium 4

Bioaerosols and respiratory health

M4.1 ATOPIC AND NON-ATOPIC RESPONSES TO FUNGAL SPORES IN ANIMALS AND HUMANS

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Introduction: Fungal spores are ubiquitous in the environment and healthy people are well adapted to cope with inhaled spores of most species. Occupational exposure levels may be much higher than outdoor levels, especially at workplaces where mouldy materials are handled. Febrile reactions are relatively common in such occupations, which usually are related to episodes with high exposures resulting in attacks of toxic and allergic alveolitis. Exposure levels in other workplaces are much lower, even below outdoor levels. However, respiratory symptoms such as Sick Building syndrome and asthma have been related to indoor environments of humid buildings. Atopy seems to play a role in these responses, while atopic disease is rare in the high exposed populations. Scientific evidence for atopic and non-atopic responses to fungal spores is therefore presented.
Methods: A literature search of experimental, clinical, and epidemiological studies of fungal spores was conducted and further references were obtained from reviewed papers.
Results: The defence against fungal spores observed in single exposure in vivo studies is dominated by non-adaptive responses. Alveolar macrophages bind fungi with innate receptors, as the TLR receptors, and phagocytise and kill the spores. In vivo studies using repeated exposures show atopic responses, as increase in eosinophilic granulocytes and IL-4, besides neutrophilic inflammation. In one study viable spores induced an atopic response whereas a non-atopic response was observed with killed spores. This is further supported by allergen production by germinating spores, and in vitro studies with dendritic cells (DC). DCs phagocytise both spores and hyphae, but these cells instruct precursor T helper cells in the lymph nodes to mature in to Th2 cells after phagocytosis of hyphae, while phagocytosis of spores leads to priming of Th1 cells.
Conclusions: Fungal spores may induce atopic and non-atopic responses that seem to depend on exposure to hyphae and/or germination of inhaled spores. As asthmatic attacks occur after exposure to relatively low spore levels, atopic responses in low exposed populations may be expected in individuals with atopic predisposition. The absence of atopic responses in highly exposed populations is a greater challenge to explain and is a hot research topic. Development of tolerance and selection are possible explanations.

M4.2 CAN OCCUPATIONAL EXPOSURE TO MICROBIAL AGENTS *REVERSE* ALLERGIC IMMUNE RESPONSES?

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Studies have shown that endotoxin exposure in childhood is associated with a reduced risk of atopy and atopic asthma. There is also experimental evidence that exposure to peptidoglycans, CpG containing DNA, and certain viruses may reduce the risk of atopic disease. Mycobacterial lipoglycans and even fungal components may play a role as well. It is commonly assumed that these protective effects only occur in *early life*. However, there is very little evidence that the early years of life are crucial. In fact, it is more likely that allergies and asthma represent a continuum rather than a fixed immulogical state, which can be both up and down regulated at any time of life depending on the level of immunoregulatory exposures. Some evidence for this is available from: (1) animal studies; (2) studies among migrants; and (3) occupational studies. Studies of migrants and specific occupational populations are very interesting in this regard since their environments often change dramatically during adulthood (in contrast to the general population whose environmental exposures are often only marginally different from that during childhood). Assuming that the immune system is not ''fixed'' after the first years of life, we hypothesise that microbial exposure may not only *inhibit* the development of atopic sensitisation and disease at any time throughout life, but may also *reverse* this process. Prospective observational studies in atopic subjects newly exposed to high levels of microorganisms through their work environment would be of great value to test this hypothesis, and could ultimately lead novel treatment for atopic disease. In this paper we present some of the evidence that microbial exposures can reverse atopic immune responses and discuss the potential of occupational studies to test this novel hypothesis.

M4.3 BIOAEROSOL EXPOSURE AND COPD: IS THERE A LINK AND WHAT ARE THE LIKELY MECHANISMS?

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The endotoxin and β-glucan concentrations in organic dust are thought to be major risk factors for the chronic neutrophilic inflammation of the airways among occupationally exposed workers. In this context, there is a large body of literature indicating that exposure to farming environments increases the risk of chronic bronchitis with a prevalence of 5% to 39% among farmers. In the European Farmers' Study, farmers in the age group 20–44 years were already at increased risk for chronic bronchitis. In a meta-analyses the summary odds ratio for chronic bronchitis among animal farmers as compared with unexposed reference populations was 2.0 (95% CI 1.7 to 2.4).

Endotoxins are also considered to be of uppermost importance in the development of ODTS, a systemic neutrophilic inflammatory reaction with flu-like symptoms. However, if workers are repeatedly exposed, some degree of tolerance seems to develop. Epidemiological studies have shown that ODTS is very common in farmers with a lifetime prevalence of 23% in pig farmers. In the past, ODTS has been considered a self-limiting, harmless syndrome. In contrast, newer studies indicate that ODTS is associated with an increased risk of chronic bronchitis in farmers. Therefore, the acute neutrophilic inflammation of the lung seems to cause a chronic neutrophilic inflammation associated with chronic symptoms in repeatedly exposed workers.

M4.4 HOW VARIABLE IS THE ATOPIC IMMUNE RESPONSE?

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Studies have shown that endotoxin exposure in childhood and at adult age is associated with a reduced risk of atopy and atopic asthma. Exposure to other microbial agents such as peptidoglycans, CpG containing DNA, may play a role as well. These observations have led to the hypothesis that microbial exposure may not only *inhibit* the development of atopic sensitisation and disease at any time throughout life, but may also *reverse* this process. This hypothesis needs to be studied in prospective designs in individuals with a high exposure to microbial agents. It also requires insight in the variability of the atopic response in individuals with allergen exposure, in the absence of high microbial agent exposures. In this paper, results will be presented on variability of skin prick test (SPT) responses in a cohort of laboratory animal (LA) workers. Five hundred and twenty nine LA workers answered a questionnaire on respiratory symptoms and occupational history and participated in skin prick testing and part of this population was followed for a period of 2–3 years. Determinants of variability in response of SPTs against rats and mice were considered, including allergen exposure. Results suggest that the background variability in SPT responses is high, and indications exist that conversion from SPT positive to negative and from SPT negative to positive are both exposure related.

M4.5 THE ROLE OF NON-ALLERGIC INFLAMMATION IN BIOAEROSOL INDUCED RESPIRATORY DISEASE

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Organic dusts cause inflammatory reactions in the tissues exposed. The lung and the cells lining the surface of the respiratory tract are a primary

target. Many receptors have been shown to react specifically on the presence of microorganisms that are ubiquitous elements in organic dusts. There is a great variability in the individual response to organic dusts. Almost 50% of Whites are hyporesponders to organic dust exposure. The diseases resulting from organic dust exposures include asthma, allergy, hypersensitivity pneumonitis, and toxic pneumonitis (organic dust toxic syndrome).

This presentation deals with the non-allergic inflammation encountered in industries with these exposures. Toxicological studies including human experimental exposures and ex vivo studies of cells are described. Cellular reactions are mediated through the attachment of, for example, LPS and β (1,3)-D-glucan to lipopolysaccharide binding protein, CD14, and toll-like receptors. The studies of the individual susceptibility on these mechanisms will be reviewed.